Remarks/Arguments

Upon entry of this response, claims 1-3 and 6-15 will be pending. Claims 4 and 5 have been previously canceled without prejudice or disclaimer. Claims 8-12, 14 and 15 have been withdrawn from further consideration pursuant to 37 CFR § 1.142(b), as being drawn a to nonelected invention. By the present response, claim 1 has been amended to define Applicants' invention with greater particularity. Support for amended claim 1 may be found at page 3, lines 15-16, and at page 11, lines 23-34 of the specification. Thus, the amendments add no new matter, being fully supported by the specification and original claims.

Claim Objections

The Examiner objected to claim 1 because the claim contains limitations, staphylococcus alpha toxin and beta toxin, heat labile toxin or pathogenic E. coli, that are recited twice within the claim. Applicants have amended claim 1 to remove the duplicative limitations, and respectfully requests withdrawal of the objection.

Rejections under 35 U.S.C. § 102(b)

Applicants respectfully traverse the rejection of claims 1, 3, 6, 7 and 13 as allegedly anticipated by Rappaport or Arciniega et al. Applicants' amended claims to an adjuvant distinguish over the disclosures of Rappaport and Arciniega by requiring an attenuated toxin having a residual toxic activity of less than one-two thousandth (<1/2000) that of the natural toxin corresponding thereto and having an activity of enhancing production of an antigen-specific antibody, and having a formalin molecule bound to a lysine residue of the toxin, which retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence.

Rappaport discloses a glutaraldehyde-treated toxin, while amended claim 1 recites a toxin bound to a formalin molecule. Applicants submit that glutaraldehyde toxoid has a structure in which each functional group at both ends of the glutaraldehyde molecule binds to a reside (e.g., lysine residues) of toxin. Thus multiple toxin molecules are bound to each other. Further, the previous report of Rappaport (Infect. Immune. 1974, Vol. 9, pp. 304-317) suggests the possibility that some proportion fo the reaction products may tend to aggregate or even polymerize (via an exposed aldehyde on the bifunctional glutaraldehyde molecule)

(page 309, right column, lines 22-26). Therefore, the attenuated toxin polypeptides of the instant invention structurally differ from the prior art glutaraldehyde toxoid.

The Examiner alleges that the toxoid taught by Rappaport is the same as that of Applicants' invention because the toxoid allegedly shares the same structural features defined by the claims. As discussed above, amended claim 1 does not share that same structural features of the prior art toxoids. It is noteworthy to mention that, as described at page 13, lines 12-15 of the specification, it is commonly accepted in the art that a high level of reduction of toxin activity does not lead to development of adjuvants with high safety because the reduction is associated with the decrease of the immuno-enhancing activity. In fact, that above-mentioned report of Rappaport discloses that complete elimination of detectable toxicity could be achieved, but with some risk of obtaining either insoluble reaction products or adversely affecting the ability of the antigen to stimulate circulating antitoxin in immunized rabbits (page 306, right column). Accordingly, since Rappaport fails to disclose each and every element of the invention, as defined by amended claim 1, Applicants respectfully submit that the disclosure of Rappaport does not establish anticipation of claims 1, 3, 6, 7 and 13 under 35 U.S.C. § 102(b).

The Examiner further asserts that Arciniega discloses all of the elements of Applicants' invention. Like Rappaport, Arciniega does not disclose an attenuated toxin having a residual toxic activity of less than one-two thousandth (<1/2000) that of the natural toxin corresponding thereto and having an activity of enhancing production of an antigen-specific antibody, and having a formalin molecule bound to a lysine residue of the toxin, which retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence. Arciniega compares the immune response in a subject to challenge by the B oligomer of Pertussis toxin with the immune response to challenge by inactivated Pertussis toxin. Arciniega demonstrates that "the B oligomer did not appear to be superior to inactivated pertussis toxin as *an immunogen*...." (Arciniega, page 1135, column 2). Applicants assert that the pertussis toxoid of Arciniega is limited to use as a specific antigen (immunogen), and thus does not have the activity of *enhancing* production of an antigen-specific antibody. Further, as discussed above, amended claim 1 does not share that same structural features of the prior art toxoids. Accordingly, since Arciniega fails to disclose each and every element of the invention, as defined by amended claim 1, Applicants

respectfully submit that the disclosure of Arciniega does not establish anticipation of claims 1, 3, 6, 7 and 13 under 35 U.S.C. § 102(b).

Applicants respectfully traverse the rejection of claims 1 and 2 as allegedly anticipated by Yamamoto or Kaper et al. under 35 U.S.C. § 102(b). Applicants' amended claims to an adjuvant distinguish over the disclosures of Yamamoto and Kaper by requiring an attenuated toxin having a residual toxic activity of less than one-two thousandth (<1/2000) that of the natural toxin corresponding thereto and having an activity of enhancing production of an antigen-specific antibody, which retains serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence.

Applicants disagree with the Examiner's assertion that Yamamoto discloses all of the elements of Applicants' invention. More particularly, Yamamoto does not disclose an adjuvant that comprises an attenuated mutant toxin, which *retains serine residues*, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence. Yamamoto discloses a nontoxic mutant of cholera toxin (CT) that is "made by *substitution of serine* with phenylalanine at position 61 of the A subunit...." (Yamamoto, Abstract). Applicants assert that the CT of Yamamoto does not anticipate the invention as described in amended claim 1 because it does not retain serine residues, glutamic acid residues, and lysine residues of the natural toxin in its amino acid sequence. Since Yamamoto fails to disclose each and every element of the invention, as defined by amended claim 1, Applicants respectfully submit that the disclosure of Yamamoto does not establish anticipation of claims 1 and 2 under 35 U.S.C. § 102(b).

Applicants disagree with the Examiner's assertion that Kaper discloses all of the elements of Applicants' invention. More particularly, Kaper does not disclose an *adjuvant* that comprises attenuated mutant toxin. Kaper discloses an attenuated *V. cholerae* strain constructed by deleting genes encoding the enterotoxin. "A plasmid has been constructed which produces only the nontoxic B subunit....This plasmid has been introduced into *V. cholerae* JBK70, after which it was found to produce B antigen but not holotoxin." (Kaper, page 658, column 1). Applicants assert that the resulting B subunit of Kaper is limited to use as a specific antigen, and thus does not have the activity of *enhancing* production of an antigen-specific antibody. Since Kaper fails to disclose each and every element of the

invention, as defined by amended claim 1, Applicants respectfully submit that the disclosure of Kaper does not establish anticipation of claims 1 and 2 under 35 U.S.C. § 102(b).

Rejections under 35 U.S.C. § 103(a)

The rejection of claims 1, 3, 6, 7, and 13 under 35 U.S.C. § 103(a), as being obvious over Rappaport or Arciniega et al. is respectfully traversed. The burden of proof in establishing a *prima facie* case of obviousness under § 103 clearly rests with the Patent Office. *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). In establishing a *prima facie* case, the Patent Office, among other things, must show that (1) the prior art would have suggested to those of ordinary skill in the art that they should make the claimed invention and (2) that the prior art would have revealed a reasonable expectation of success. *In re Vaeck,* 947 F.2d 488, 493 (Fed. Cir. 1991). "Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure." *Id.* Thus, "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed." *In re Kotzab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000). Further, when relying on the knowledge of persons of ordinary skill in the art, the Patent Office must "explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination." *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

To date, the Patent Office has failed to provide objective evidence of any suggestion or motivation in the prior art to modify the particular references cited by the Office. Instead, the Office has simply recited elements gleaned from the references and stated that these elements would have been obvious to one skilled in the art. It is well settled that the Patent and Trademark Office cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. *SmithKline Diagnostics, Inc. v. Helena Laboratories Corp.*, 859 F.2d 878, 887 (Fed. Cir. 1988). In addition, it is now well established that "[b]road conclusory statements regarding the teaching of multiple references standing alone are not 'evidence'." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999); see also *In re Kotzab*, 217 F.3d at 1370. "Th[e] factual question of motivation is material to patentability, and [can] not be resolved on subjective belief and unknown authority." *In re Sang Su Lee* 277

F.3d at 1343-44. Without such objective evidence to combine the references, it is inferred that the references were selected with the assistance of hindsight. *In re Rouffet*, 149 F.3d at 1358. It is well-established that the use of hindsight in the selection of references that comprise a case of obviousness is forbidden. *Id.*

The Examiner alleges that it would have been obvious to one of ordinary skill in the art to optimize the toxoids taught by Rappaport and Arciniega by reducing the level of toxin activity as a matter of routine experimentation with a reasonable expectation of success. The remarks above distinguishing Applicants' invention over the disclosures of Rappaport and Arciniega apply equally here. Neither Rappaport nor Arciniega disclose use of an attenuated toxin as *an adjuvant*, and therefore do not suggest an attenuated toxin having an activity of *enhancing* production of an antigen-specific antibody. Both disclosures demonstrate use of attenuated toxins as antigens for eliciting immunogenic responses in subjects. Those of skill in the art would understand that a toxoid useful for its antigenic properties is not guaranteed to have adjuvant activity towards other antigens. Thus, without a suggestion of specifically using the disclosed toxoids as adjuvants to vaccine antigens, there could be no expectation of success. Further, the above-mentioned report of Rappaport discloses various disadvantages of Formalin toxoid (page 304). However, in contrast to such knowledge in the art, Applicants have found that formalin treatment successfully produces highly attenuated toxin while retaining adjuvant activity. Applicants submit that as amended, claim 1 is not obvious over the disclosures of Rappaport or Arciniega et al.

Accordingly, it is respectfully submitted that the Examiner has not met the burden of proving *prima facie* obviousness under 35 U.S.C. § 103(a), and withdrawal of the rejections is respectfully requested.

Conclusion

In view of the above remarks, it is submitted that the claims are in condition for allowance, and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this matter.

Enclosed is check #567035 in the amount of $950.00 to cover the Three-Month Extension of Time fee in connection with the filing of this paper. The Commissioner is hereby authorized to charge any additional fee, or credit any overpayments, to Deposit Account No. 50-1355.

Respectfully submitted,

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